REMARKS AND RESPONSES

Claims 1, 4 and 25 are pending. Claims 2-3, and 5-24 are canceled.

1. Amendment to the Claims

Claim 25 is amended to depend from claim 1. No new matter is added.

2. Claim Objections

Claim 25 is objected to under 37 CFR § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 25 is amended to depend from claim 1. Thus, the objection is moot.

3. Rejection of Claim 25 under 35 U.S.C. § 112, second paragraph

Claim 25 is rejected because there is insufficient antecedent basis for the term "cancer". As noted above, claim 25 is amended to depend from claim 1 which supplies the requisite antecedent basis. Accordingly, the rejection is overcome.

4. Rejection of Claim 1 under 35 U.S.C. § 112, second paragraph

Claim 1 is rejected as allegedly vague and indefinite for reciting "invasive ability" as the specification allegedly fails to teach an active step for determining an "invasive ability". Applicants respectfully traverse this rejection for at least the reasons provide below.

4.1 Analysis

Definiteness of claim language must be analyzed, not in a vacuum, but in light of three criteria: (a) the content of the particular application disclosure; (b) the teachings of the prior art; and (c) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made (MPEP § 2173.02).

With regard to the first criterion, the specification as originally filed provides a method for determining the ability of cell lines to invade a defined basement membrane matrix (See paragraph 80 of the published application US2003/0152923A1). The specification provides, in pertinent part:

> Selected cell lines were tested for their ability to invade a defined basement membrane matrix. Tumor cells ($1x10^5$) were seeded into the upper wells of the membrane invasion culture system (MICS) chamber (Hendrix et al. "A simple quantitative assay for studying the invasive potential of high and low human metastatic variants" Cancer Lett. 38:137-147, 1987; incorporated herein by reference) onto collagen/laminin/gelatin-coated (Sigma) polycarbonate membranes containing 10 μm pores (Osmonics, Livermore, Calif.) containing 1.times. Mito+ Serum Extender (Becton Dickinson). After 24 h of incubation at 37° C., the cells that invaded each membrane were collected, stained and counted as described (Hendrix et al. "Role of intermediate filaments in migration, invasion and metastasis" Cancer Metastasis Rev. 15:507-525, 1996; incorporated herein by reference). Percent invasion was corrected for proliferation and calculated as (total number of invading cells/total number of cells seeded) x 100.

Applicants submit that the above-described method and references cited therein describe at least one method for determining invasive ability that was known in the art at the time the present application was filed.

With regard to the second criterion, the prior art teaches methods of determining invasive ability. The present specification cites and incorporates by reference Hendrix et al. "A simple quantitative assay for studying the invasive potential of high and low human metastatic variants" Cancer Lett. 38:137-147, 1987, and Hendrix et al. "Role of intermediate filaments in migration, invasion and metastasis" Cancer Metastasis Rev. 15:507-525, 1996, as references which specifically teach methods of determining invasive

ability of cells. Thus, the prior art provides at least one method for determining invasive ability of cells.

Turning now to the third criterion, one of ordinary skill in the art at the time the invention was made would understand claim 1 to include comparing the expression of *Wnt5a* in a test sample to *Wnt5a* expression in a tumor having less than about 3.5% invasive ability. In view of the cited references by Hendrix et al. and the teaching of the specification, one of ordinary skill in the art would be able to determine invasive ability of a cell.

Because the specification specifically provides at least one method for determining invasive ability of a tumor cell, and because the Hendrix et al. references were published long before the filing date of the present application, Applicants submit that one of ordinary skill would be able to determine invasive ability, and therefore, claim 1 satisfies the requirements of 35 U.S.C. § 112.

5. Rejection of Claim 1 under 35 U.S.C. § 112, first paragraph

Claim 1 is rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does not contain a written description of the claimed invention. Applicants respectfully traverse this rejection.

Claim 1 has written support throughout the specification as originally filed, and particularly in Table 1. The Office Action concludes that there is no clear support for "less than about 3.5% invasive ability." As an initial matter, Applicants note that Table 1 includes data from various melanoma cell lines and compares various characteristics of these cell lines. For example, data comparing invasive ability, vasculogenic mimicry, gel contractions, cell motility, and the ability to close an in vitro scratch wound are provided. The

legend to Table 1 provides information on how the data for each characteristic was obtained. With regard to invasive ability, the legend indicates that the data refers to the ability to invade a defined basement matrix. A more detailed explanation of Table 1 is found in paragraphs 77 to 80 of the specification as originally filed.

As described in the specification, expression patterns from 31 melanomas were used to group cells according to similar expression patterns of certain genes (paragraph 54). The cells in the melanoma primary cluster group (Group A) showed reduced invasive ability compared to the non-clustered melanoma cells (Group B)(see Table 1). Uveal melanoma samples characterized for properties related to metastasis (see paragraph 64 of the specification) were also assayed. The data in Fig. 2B show that gene expression patterns from uveal melanoma cells (C918/OCM-1A and MUM2B /MUM2C) correlate with the gene expression of the non-clustered melanoma cells. Specifically, *Wnt5a* is expressed at high levels in both metastatic uveal melanoma cells and Group B cells.

Table 1 shows the data from melanoma samples. In particular, UACC-903 cells in Group B or the non-cluster melanoma cells show a range from 3.8 ± 0.3% to 10.7 ± 0.03% invasive ability. This range is higher than about 3.5% invasive ability, as recited in claim 1. Group A melanoma cells show invasive ability from 2.1 ± 0.2% to 3.2 ± 0.2%, a range with is lower than about 3.5% invasive ability. Thus, Table 1 supplies written description for "less than about 3.5% invasive ability." Moreover, Group B melanoma cells are distinguishable from Group A melanoma cells in part because Group B melanoma cells show a greater invasive ability, and are therefore more aggressive. Figure 2B

shows that Group B cells strongly express *Wnt5a*; whereas, Group A cells weakly express *Wnt5a*. Thus, the specification provides written description for a method of diagnosing an aggressive form of cancer comprising providing a genetic sample from a test sample of a tumor, and analyzing expression of *Wnt5a* wherein increased expression of *Wnt5a* in the test sample compared to *Wnt5a* expression in a tumor having less than about 3.5% invasive ability indicates the tumor is aggressive and has the potential to metastasize. Accordingly, Applicants respectfully request that the rejection of claim 1 be withdrawn.

6. Rejection of Claims 4 and 25 under 35 U.S.C. § 112, first paragraph

Claims 4 and 25 are also rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

As noted above, Table 1 of the present specification includes data concerning vasculogenic mimicry. Paragraphs 77 through 78 of the specification describe protocols for determining vasculogenic mimicry. The data from tumor cells exhibiting vasculogenic mimicry and those that do not are compared in Table 1. In particular, Group A cells have no detectable or no vasculogenic mimicry; whereas, a majority of Group B cells do exhibit vasculogenic mimicry. As noted above, Group B cells are more aggressive than Group A cells, and Figure 2B shows that Group B cells express higher levels of *Wnt5a* than Group A cells. Therefore, Applicants respectfully submit that the specification provides written description supporting the step of determining expression of *Wnt5a* wherein increased expression of *Wnt5a* in the test sample compared to *Wnt5a* expression in a tumor having non-

detectable or no vasculogenic mimicry indicates the tumor is aggressive. Applicants respectfully request that the rejection of claim 4 be withdrawn.

With regard to the alleged lack of enablement, Applicants disagree that the limitations in the claims alter the scope of the disclosure as originally filed. Indeed, when considered as a whole, the disclosure is generally directed to distinguishing aggressive forms of cancer from other less aggressive forms or cancer. The data in Table 1 as well as the specification generally enable the claims as presented. Applicants respectfully submit that one of skill in the art would understand the data of Table 1 to include phenotypic indicators useful for distinguishing aggressive forms of cancer. Moreover, one of skill in the art would also recognize Fig. 2A as providing genetic expression characteristics for distinguishing aggressive forms of cancer. The specification recites, "As predicted from the analysis of their gene expression patterns, melanomas within the major cluster [Group A] had reduced motility (P=0.0063), invasive ability (P=0.0055) and vasculogenic mimicry in comparison with melanomas outside the major cluster" (see last sentence of paragraph 65). Accordingly, Applicants submit that the disclosure as originally filed includes adequate written description of the claims and enables the claims. Therefore, the rejection of claim 4 should be withdrawn.

With regard to claim 25, claim 25 is amended to depend from claim 1. Accordingly, the rejection of claim 25 is moot.

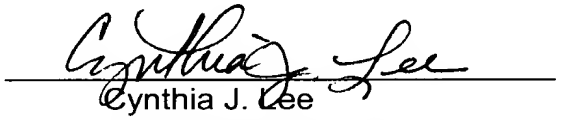
Conclusion

For at least the foregoing reasons, Applicants submit that all rejections and objections have been addressed or rendered moot and that claims 1, 4 and 25 are in condition for allowance.

If the Examiner believes that a telephone conference would expedite the examination of the above-identified patent application, the Examiner is invited to call the undersigned.

No fee is believed to be due in connection with this amendment and response. If, however, any fee is believed to be due, the Commissioner is hereby authorized to charge any such fee to deposit account No. 50-1078.

Respectfully submitted,



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